NEUROLEPTICS OF THE 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*] THIEPIN SERIES AND RELATED SUBSTANCES: PIPERAZINE-ALKYLATED HOMOLOGUES OF OCTOCLOTHEPIN AND METHIOTHEPIN; 5,5-DIMETHYL-10,11-DIHYDRO-5*H*-DIBENZO[*b,f*] SILEPIN ANALOGUE OF PERATHIEPIN*

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Acetylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin and subsequent reduction was used to prepare the N-ethyl homologue of octoclothepin (*II*). The N-isopropyl analogue *III* was obtained from the same starting compound by alkylation with isopropyl *p*-toluenesulfonate. Substitution reactions of 8,10-dichloro- and 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]-thiepin with 1-(tert-butyl)piperazine, 2-methylpiperazine and *trans*-2,5-dimethylpiperazine resulted in *IV*, *IX*, *XII*, *XV* and in the product of double alkylation *XVI*. Compounds *IX* and *XII* were converted *via* the N-formyl derivatives to the methyl homologues of methiothepin and octoclothepin (*XI* and *XIV*). Starting from 5,5-dimethyl-10,11-dihydro-5*H*-dibenzo[*b,f*]silepin (*XVIII*) the dimethylsilepin analogue of perathiepen (*XVII*) was synthesized. Of the compounds prepared, only the N-substitution homologues of octoclothepin *II*-*IV* display a high degree of neuroleptic activity. All the three compounds are more potent than octoclothepin in the catalepsy test in rats.

Octoclothepin, *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[1,2] (*I*) remains the prototype of sedatively and cataleptically highly effective neuroleptics of the 10-piperazinodibenzo[*b,f*]thiepin series; it resembles its 8-methylthio analogue methiothepin[3]. In spite of the abundance of data on the N-substitution analogues of the two compounds[4-10] and hence on the effect of replacing the piperazine N^4-methyl group by other substituents on activity there had been no information on the effect of replacing this methyl with the nearest higher alkyls. We have described some time ago[11] the N-ethyl analogue of perathiepin, *i.e.* a compound unsubstituted in position 8 but its pharmacological evaluation was restricted to tests of central depressant activity (to bring about ataxia in mice a four-fold higher dose was needed than with perathiepin) so that the information is only fragmentary.

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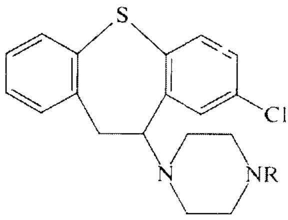
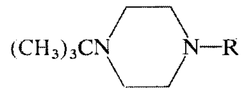
In the first section of this work the preparation and pharmacology of ethyl, isopropyl and tert-butyl analogues of octoclothepin (*II*–*IV*) are described.



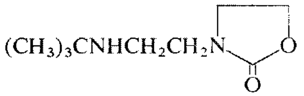
I, R = CH_3
II, R = CH_2CH_3
III, R = $CH(CH_3)_2$
IV, R = $C(CH_3)_3$
V, R = $COCH_3$

In the preparation of the N-ethyl analogue of octoclothepin (*II*) we used the same method as in the preparation of the N-ethyl analogue of perathiepin[11]. Acetylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[4] with acetic anhydride in acetic acid yielded the acetyl derivative *V* which was reduced with lithium aluminium hydride in a mixture of tetrahydrofuran and ether. For preparing the N-isopropyl analogue *III* one could consider the substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1] with 1-isopropylpiperazine[12] but, due to technical difficulties, we preferred alkylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[4] with isopropyl *p*-toluenesulfonate[13].

The synthesis of the tert-butyl derivative *IV* was motivated not only by the fact that it is one of the nearest homologues of octoclothepin (*I*) but also by the finding[14,15] that one of the biotransformation pathways of octoclothepin and simultaneously of its inactivation is its N-demethylation to 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[4]. This demethylation takes place mostly by enzymic oxidation at the carbon atom adjacent to the nitrogen atom, *i.e.* at N-methyl. The N-(hydroxymethyl) derivative formed is then hydrolyzed to the demethyl compound. The possibility cannot be excluded that a role is played here by a shift of the oxygen atom in the molecule of the N-oxide to the neighbouring carbon atom, the octoclothepin N-oxide thus formed[16] having been identified as one of the metabolites of octoclothepin[14]. With the N-(tert-butyl) derivative *IV* this possibility is seemingly eliminated and the compound should be resistant to this metabolic mechanism. During synthesis of *IV* we were thus influenced much like Kuntzman and coworkers[17] in their study of N-(tert-butyl)norchlorocyclizine and like Sternbach[18] in the synthesis of the N-(tert-butyl) analogue of diazepam. However, in the meantime, work on N-(tert-butyl)norchlorocyclizine[19,20] demonstrated that such considerations are erroneous and that the compound is metabolically N-dealkylated to norchlorocyclizine; this is explained by assuming one of the methyls of tert-butyl to be oxidized *via* the primary alcohol to the acid which is decarboxylated to the N-isopropyl derivative capable of N-dealkylation in the usual way.



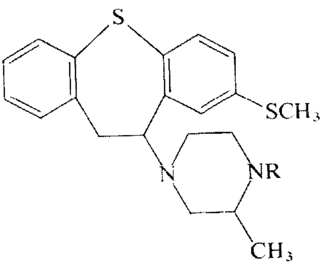
VI, R = $COOC_2H_5$
VII, R = H



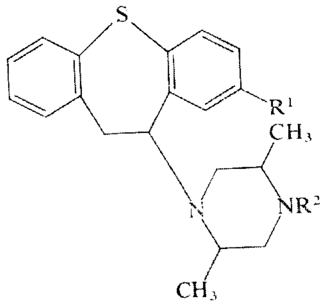
VIII

Difficulties appeared in the attempts to synthesize *IV*: alkylation of 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*] thiepin[4] with N-(tert-butyl) *p*-toluenesulfonate (prepared "*in situ*") and alkylation of the same starting compound metallated before with phenyllithium in a mixture of ether and benzene with the aid of tert-butyl bromide never resulted in characterized products. The possible intermediate 1-(tert-butyl)piperazine (*VII*) had not been known from the literature and an attempt at its synthesis by a reaction of N,N-bis(2-chloroethyl)amine[21,22] with tert-butylamine was not successful. Finally we used the procedure starting from ethyl N,N-bis(2-chloroethyl)carbamate[23,24]. Its reaction with tert-butylamine in boiling 1-butanol in the presence of potassium carbonate gave rise to a mixture of compounds, which was distilled to yield 1-(tert-butyl)-4-(ethoxycarbonyl)piperazine (*VI*) and a higher-boiling substance $C_9H_{18}N_2O_2$ of basic character (it forms a crystalline hydrochloride) which was identified with the aid of spectra as 3-(2-tert-butylaminoethyl)oxazolidine-2-one (*VIII*). The fact that the distillation product contained the hydrochloride of *VIII* which could not be present in the mixture before distillation indicates that *VIII* is formed only during the distillation of the crude product which probably contains the reactive product of monoalkylation, *i.e.* ethyl N-(2-tert-butylaminoethyl)-N-(2-chloroethyl)carbamate. The formation of *VIII* is not surprising as during the reaction of N,N-bis(2-chloroethyl)amine with carbon dioxide the 2-oxazolidinone derivative of a similar type is formed[25]. Alkaline hydrolysis of carbamate *VI* using a high concentration of potassium hydroxide yielded 1-(tert-butyl)piperazine (*VII*) which underwent a substitution reaction with 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[1] in boiling chloroform to the desired product *IV*.

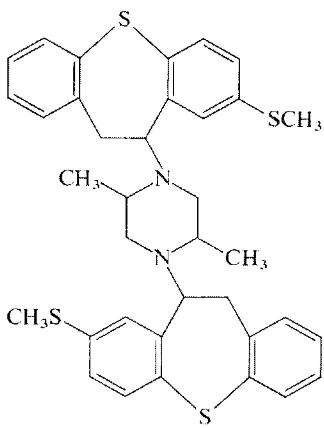
In another section of the work we took up the analogues of octoclothepin and methiothepin C-methylated in the piperazine ring and in this connection we prepared *IX*–*XVI*. The starting compounds here were 2-methylpiperazine and *trans*-2,5-dimethylpiperazine. Reaction of 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]-thiepin[3] with a greater excess of 2-methylpiperazine in boiling chloroform yielded an amorphous base which formed crystalline maleate. It is assumed that the alkylation took place at the sterically more accessible nitrogen atom (in analogy with the literature data on monoacylation of 2-methylpiperazine with ethyl chloroformate[26] and monoalkylation with the aid of chloroalkanols[27]) and the product is formulated as *IX*. Even if the alkylation had been fully selective (the entering substituent is sterically rather demanding) another centre of asymmetry would have been formed and product *IX* would have been at least a mixture of two racemates. The product was formylated by heating with ethyl formate in an autoclave at 130–140°C and the crude amide *X* was reduced with lithium aluminium hydride. Again an amorphous (and probably nonhomogeneous) base *XI* was obtained which yielded crystalline maleate.



IX, R = H
X, R = CHO
XI, R = CH_3

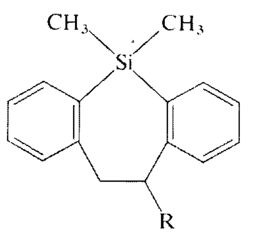


XII, R^1 = Cl, R^2 = H
XIII, R^1 = Cl, R^2 = CHO
XIV, R^1 = Cl, R^2 = CH_3
XV, R^1 = SCH_3, R^2 = H

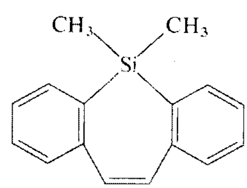


XVI

During the reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] with *trans*-2,5-dimethylpiperazine the situation is similar to the preceding case: both nitrogen atoms of the starting base are equivalent but the molecule acquires two new centres of asymmetry, the configuration of which is mutually fixed; one must again expect the formation of two racemates. In agreement with this, an amorphous base is again formed, the maleate of which is crystalline but nonhomogeneous. The base released from the partly purified maleate crystallized and, after recrystallization, behaves like a homogeneous compound during chromatography on a thin layer of alumina. Formylation of the crystalline base *XII* with ethyl formate yielded the crystalline amide *XIII* which was reduced like in the preceding case to *XIV*; Its base is again amorphous and was characterized only by its ^{1}H-NMR spectrum. Finally, 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin[3] reacted with *trans*-2,5-dimethylpiperazine. The amorphous base *XV* obtained formed a crystalline maleate and, as a by-product, a minute amount of a poorly soluble and high-melting base was obtained which, on the basis of analysis, is assumed to be a doubly alkylated product *XVI* (for analogy see[4]). All the substitution reactions shown are accompanied by eliminations, the products of which are 2-chlorodibenzo[*b,f*]thiepin[1] and 2-(methylthio)dibenzo[*b,f*]thiepin[3]; their isolation is not described in the experimental section.



XVII, R = N(piperazine)NCH$_3$
XVIII, R = H
XIX, R = Br



XX

In this context we describe the synthesis of the 5,5-dimethyl-10,11-dihydro-5*H*-dibenzo[*b,f*]silepin analogue of perathiepin, *i.e.* compound *XVII*. It followed from our previous work that in position 5 of the dibenzo[*b,f*]thiepin skeleton one can re-replace in the neuroleptically active 10-piperazine derivatives the sulfur atom with a methylene group[28], with an atom of oxygen[29] or of selenium[30] without altering the type of pharmacodynamic activity. Differences between the individual isosters are only quantitative. From this point of view it was of interest to examine the analogue with a silicon atom in position 5. Conditions for the synthesis of a compound of this type arose in 1971 when a simple preparation[31–33] of 5,5-dimethyl-10,11-dihydro-5*H*-dibenzo[*b,f*]silepin (*XVIII*) was described. One of the procedures was reproduced here[33], compound *XVIII* was converted by bromination with N-bromosuccinimide in tetrachloromethane to the 10-bromo derivative *XIX* (ref.[31]) which was processed in the crude state by a reaction with 1-methylpiperazine. An oily base was obtained (*XVII*) which formed a crystalline dimaleate. Base *XVII* liberated from this salt was characterized by its ^{1}H-NMR spectrum. As a by-product there was a neutral oil, the boiling point of which agrees with literature data[33] for 5,5-dimethyl-5*H*-dibenzo[*b,f*]silepin (*XX*) which was formed as a product of a parallel elimination reaction; according to the ^{1}H-NMR spectrum the compound is not completely homogeneous.

Most of the piperazine derivatives prepared here were subjected to an orientation pharmacological screening for expected neuroleptic activity. The compounds were applied in the form of salts parenterally or orally and acute toxicity for mice, the incoordinating effect in the rotating-rod test in mice and cataleptic activity in rats were determined. The results obtained are summarized in the usual way in Table I which includes octoclothepin[1,2,4](I), methiothepin[3,4] and perathiepin[11,30] as standards. The following structure-activity relationships could be established.

1) All the three nearest N-substitution homologues of octoclothepin (*II*–*IV*) resemble the parent compound by their toxicity, their central depressant action being 2–6 times lower but their cataleptic potency 2–3 times higher. The most effective compound is the N-isopropyl derivative *III* but it is also most toxic. From the point of view of the therapeutical index, the N-ethyl derivative *II* appears to be most interesting.

2) Of the C-methylated piperazine derivatives one can consider seriously only the ditertiary amine *XI* which can be compared with methiothepin administered *p.o.*; the compound is about equally toxic, three times weaker as central depressant and twice weaker cataleptically. One can conclude that C-methylation of the piperazine ring in position 3 has a slight unfavourable effect in the present series of compounds as to their depresssant and cataleptic activities. In view of the complication with another centre of symmetry and the probable inhomogeneity of the compound under investigation the conclusion must be treated with caution.

3) Compounds *IX* and *XV* as secondary amines were not expected to be very effective on the basis of existing experience[4,11,16,34] (an exception[35]); indeed, they have no cataleptic activity and are slightly active as central depressants.

4) The silepin analogue *XVII* can be compared only with parenterally administered perathiepin[11,30]; they are similar only with respect to their toxicity. As a central depressant the silicon derivative is weaker by two orders of magnitude than perathiepin and in the catalepsy test it shows no signs of effect even at a dose which represents the ED_{50} for perathiepin. Replacement of the sulfur atom with the dimethylsilane fragment thus liquidates the character of pharmacodynamic activity.

The compounds prepared were tested by Dr J. Turinová and Dr A. Čapek (bacteriological department of this institute) for antimicrobial activity *in vitro* toward a standard set of microorganisms. Table II shows the minimum inhibitory concentrations of compounds that showed some activity. One should mention the broad antimicrobial spectrum of *III* and its high activity against cocci. All the compounds tested show a clear antituberculotic activity. Compounds *IX* and *XV* were tested *in vivo* in mice infected with *Escherichia coli* but their activity could not be confirmed here.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; samples were dried at about 0·5 Torr over P_2O_5 at room temperature or at a raised

TABLE I

Pharmacological Properties of Prepared Piperazine Derivatives (mg/kg)

Compound[a]	Mode of application[b]	Acute toxicity LD_{50}[c]	Rotating rod ED_{50}[d]	Catalepsy ED_{50}[e]
II-MS	*i.v.*	62	0·17	0·76
III-2 MS	*i.v.*	41·5	0·10	0·70
IV-2 MS	*i.v.*	73	0·4	1·3
IX-M	*p.o.*	—	15·5	>50[f]
XI-M	*p.o.*	110	6·6	17
XV-M	*p.o.*	>500[g]	17·0	[h]
XVII-2 M	*i.v.*	49	9·6	[i]
I[j]	*i.v.*	46	0·06	2·4
I	*p.o.*	78	2·2	4·3
MET[k]	*i.v.*	51	0·09	2·0
MET	*p.o.*	94	1·9	10·5
PER[m]	*i.v.*	42·3	0·19	10·0
PER	*p.o.*	62·7	2·4	45

[a] MS methanesulfonate, M maleate; the compounds are shown as the salts administered, the doses refer to the corresponding bases. [b] *i.v.* intravenously, *p.o.* orally. [c] Mean lethal doses from the estimation of acute toxicity for mice. [d] Mean effective doses bringing about ataxia in mice in the rotating-rod test at the time of maximum effect. [e] Mean effective doses bringing about catalepsy in rats; if *i.v.* is shown, intraperitoneal administration was used in this particular test. [f] The dose of 50 mg/kg brings about catalepsy in 30% animals. [g] The dose of 500 mg/kg is lethal for only 30% animals. [h] The compound was administered at the high dose of 50 mg/kg; there was no sign of effect. [i] The compound was administered at the dose of 10 mg/kg and had no effect. [j] Octoclothepin; applied parenterally as methanesulfonate, orally as maleate[1,2]. [k] Methiothepin[3]; applied as maleate. [m] Perathiepin[11]; applied as maleate.

temperature (100°C at most). The IR spectra (in KBr unless stated otherwise) were recorded in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) usually in a ZKR 60 (Zeiss, Jena) spectrometer, a few of them on a Tesla BC 487 (80 MHz) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on alumina.

10-(4-Acetylpiperazino)-8-chloro-10,11-dihydrodibenzo[*b*, *f*]thiepin (*V*)

Acetic anhydride (5·0 g) was added to a solution of 5·0 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*, *f*]thiepin[4] in 30 ml acetic acid and, after standing for 12 h at room temperature, the mixture was refluxed for 3 h under stirring (a 140–150°C bath). The volatile components were then evaporated in *vacuo*, the residue was dissolved in 50 ml benzene and the solution was shaken with 50 ml 3M-HCl. The separated oily hydrochloride was combined with the acid aqueous phase and made alkaline with NH_4OH. The liberated base was isolated by extraction with benzene; 4·6 g (81%), m.p. 178°C (methanol). For $C_{20}H_{21}ClN_2OS$ (372·9) calculated: 64·42% C, 5·67% H, 9·51% Cl, 7·51% N, 8·60% S; found: 64·49% C, 5·92% H, 9·45% Cl, 7·22% N, 8·55% S.

8-Chloro-10-(4-ethylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepin (*II*)

A solution of 3·9 g *V* in a mixture of 60 ml tetrahydrofuran and 40 ml ether was added dropwise to a solution of 1·5 g $LiAlH_4$ in 40 ml ether over a period of 40 min. The mixture was refluxed for 8 h, cooled, decomposed by adding dropwise 1·5 ml water, 1·5 ml 15% solution of NaOH and 5 ml water; after 1 h of stirring the solid was filtered and washed with ether. The filtrate was

TABLE II

Antimicrobial Activity of Prepared Piperazine Derivatives *in vitro* (minimum inhibitory concentrations in μg/ml are shown)

Compound[a]	1[b]	2	3	4	5	6	7	8	9	10	11
II-MS	50	50	50	—	—	—	25	100	50	100	100
III-MS	6·25	6·25	25	150	100	100	25	100	50	100	100
IV-2 MS	—	50	—	—	—	—	<5	100	100	100	100
IX-M[c]	12·5	—	12·5	50	50	50	25	—	—	—	—
XI-M	12·5	—	12·5	—	—	—	12·5	125	62·3	—	125
XV-M[c]	12·5	—	12·5	100	100	100	12·5	—	—	—	—
XVII-2 M	25	—	25	—	—	—	12·5	—	—	—	—

[a] MS methanesulfonate, M maleate. [b] 1 *Streptococcus* β-*haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Pseudomonas aeruginosa*, 5 *Escherichia coli*, 6 *Proteus vulgaris*, 7 *Mycobacterium tuberculosis* H37Rv, 8 *Saccharomyces pasterianus*, 9 *Trichophyton mentagrophytes*, 10 *Candida albicans*, 11 *Aspergillus niger*. [c] Also active against *Klebsiella pneumoniae*, 50; *Salmonella typhi abdominalis*, 50.

dried with $MgSO_4$ and evaporated; 3·32 g (88%) oily base. Neutralization with methanesulfonic acid in ethanol and addition of ether yielded the crystalline methanesulfonate, m.p. 188–190°C (acetone–ether). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·40 (bs, 1 H, SO_3H), 7·00–7·65 (m, 7 H, aromatic protons), 2·37 (s, 3 H, CH_3SO_2), 1·29 (t, 3 H, C—CH_3), 2·50–4·20 (m, $ArCH_2CHAr$ and 5 NCH_2). For $C_{21}H_{27}ClN_2O_3S_2$ (455·0) calculated: 55·43% C, 5·98% H, 7·79% Cl, 6·16% N, 14·09% S; found: 55·71% C, 6·15% H, 7·67% Cl, 6·22% N, 13·92% S.

1-Isopropylpiperazine

This was prepared by hydrolysis of 1-ethoxycarbonyl-4-isopropylpiperazine[12] (b.p. 103–107°C/ /0·8 Torr) with boiling 20% hydrochloric acid in a yield of 78%, b.p. 185–195°C (ref.[12] reports 194°C). Neutralization with maleic acid in ethanol led to dimaleate, m.p. 158–160°C (ethanol). For $C_{15}H_{24}N_2O_8$ (360·4) calculated: 49·99% C, 6·71% H, 7·77% N; found: 49·78% C, 6·62% H, 7·70% N.

8-Chloro-10-(4-isopropylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepin (*III*)

A mixture of 10·8 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*, *f*]thiepin[4], 15·8 g isopropyl *p*-toluenesulfonate[13] and 10 ml 2-propanol was stirred for 3 h at 80°C. After cooling, it was diluted with water, made alkaline with sodium hydroxide and extracted with benzene. The extract was washed with water, shaken with excess 3M-HCl, the precipitated hydrochloride was filtered and washed with benzene. Treatment with NH_4OH liberated a base which was extracted with benzene; 7·9 g (65%) viscous oil. The rest of the starting compound was removed by chromatography on a column of 250 g Al_2O_3, using elution with chloroform; 5·8 g purified base. ^{1}H-NMR spectrum: δ 7·79 (mcd, J = 2·5 Hz, 1 H, 9-H), 6·85–7·60 (m, 6 H, remaining aromatic protons), 3.00–4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·60 (m, 9 H, 4 NCH_2 and NCH), 1·01 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). Bismethanesulfonate, m.p. 182°C (ethanol). For $C_{23}H_{33}ClN_2O_6S_3$ (565·2) calculated: 48·88% C, 5·88% H, 6·27% Cl, 4·96% N, 17·02% S; found: 48·60% C, 6·00% H, 6·26% Cl, 5·09% N, 16·82% S.

1-(Tert-butyl)-4-(ethoxycarbonyl)piperazine (*VI*)

A mixture of 72·8 g ethyl N,N-bis(2-chloroethyl)carbamate[24] (b.p. 107–111°C/2 Torr), 37·3 g tert-butylamine, 150 ml 1-butanol and 2·0 g NaI was refluxed under stirring for 11 h. Then it was combined with 23·6 g K_2CO_3 and refluxed for further 8 h. The addition of 23·6 g K_2CO_3 was then twice repeated, refluxing for 8 h between and for 5 h after the additions. The mixture was cooled, filtered, the filtrate was evaporated *in vacuo*, the residue was diluted with benzene and the precipitated portion was again filtered. The basic product was extracted from the filtrate by shaking with 100 ml 20% hydrochloric acid, the acid aqueous phase was made alkaline with 50% NaOH and the bases were isolated by extraction with benzene. A total of 47 g liquid boiling diffusely at 110–155°C/1·2–3·5 Torr was obtained. Distillation yielded 15·5 g (21%) desired base *VI*, boiling at 102–104°C/1·5 Torr. For $C_{11}H_{22}N_2O_2$ (214·3) calculated: 13·07% N; found: 13·16% N. On continuing the distillation, a total of 12·5 g compound boiling at 125–128°C/1·5 Torr was obtained and it was identified as 3-(2-tert-butylaminoethyl)oxazolidin-2-one (*VIII*). IR spectrum: 1227, 1242, 1266 (C—O—C), 1748 (CO of cyclic carbamate), 3280 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 4·35 (t, J = 7·0 Hz, 2 H, CH_2CO in a ring), 3·64 (t, J = 7·0 Hz, 2 H, CH_2N in a ring), 3·35 and 2·86 (2 t, 4 H, N—CH_2CH_2—N), 1·35 (bs, 1 H, NH), 1·12 (s, 9 H, 3 CH_3 of tert-butyl). For $C_9H_{18}N_2O_2$ (186·3) calculated: 15·04% N; found: 15·20% N. Addition of ether to the distillation residue resulted in the precipitation of 1·5 g hydrochloride of *VIII*, m.p. 248 to

249°C under decomposition (aqueous ethanol). IR spectrum: 1272 (C—O—C), 1738 (CO of cyclic carbamate), 2430 cm^{-1} (NH_2^+). For $C_9H_{19}ClN_2O_2$ (222·7) calculated: 48·53% C, 8·60% H, 12·58% N; found: 48·31% C, 8·52% H, 12·72% N.

1-(Tert-butyl)piperazine (*VII*)

A mixture of 16·8 g *VI*, 20 g KOH and 25 ml ethanol was refluxed under stirring for 4 h (bath temp. 120°C). After cooling, it was diluted with 20 ml water and the base was isolated by extraction with benzene. Processing of the extract led to 9·1 g (82%) base *VII*, boiling at 73—75°C/12 Torr, which solidified on standing to a compound melting at 32—35°C. For characterization, the dipicrate was prepared in the usual way and crystallized from a mixture of acetone and ethanol; on heating it darkens at 260—290°C and does not melt up to 300°C. For $C_{20}H_{24}N_8O_{14}$ (600·5) calculated: 40·01% C, 4·12% H, 18·66% N; found: 40·11% C, 4·10% H, 18·46% N. During the press of this paper a synthesis of *VII* has been described[36] starting from N,N-bis(2-chloroethyl)-tert-butylamine and proceeding via 1-benzyl-4-(tert-butyl)piperazine; b. p. 66—70°C/12 Torr, m.p. 35—40°C.

10-(4-Tert-butylpiperazino)-8-chloro-10,11-dihydrodibenzo[*b*, *f*]thiepin (*IV*)

A mixture of 3·0 g 8,10-dichloro-10,11-dihydrodibenzo[*b*, *f*]thiepin[1], 8·5 g *VII* and 10 ml chloroform was refluxed for 6 h. After cooling, it was diluted with benzene and the solution was washed with water. The benzene phase was shaken with excess 10% hydrochloric acid, the precipitated hydrochloride was filtered and suspended in the acid aqueous phase. Treatment with NH_4OH liberated a base which was extracted with benzene; 3·88 g (94%), m.p. 129—131°C (ethanol). ^{1}H-NMR spectrum: δ 7·68 (mcs, J = 2·0 Hz, 1 H, 9-H), 7·48 (m, 1 H, 4-H), 7·34 (d, J = 8·5 Hz, 1 H, 6-H), 7·05—7·30 (m, 3 H, 1,2,3-H_3), 7·00 (mcd, J = 8·5; 2·0 Hz, 1 H, 7-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·64 (bs, 8 H, 4 NCH_2), 1·06 (s, 9 H, 3 CH_3 of tert. butyl). For $C_{22}H_{27}$ . . ClN_2S (387·0) calculated: 68·28% C, 7·03% H, 7·24% N; found: 68·17% C, 7·28% H, 6·95% N.

Bis(methanesulfonate), m.p. 246·5—247°C under decomposition (aqueous ethanol–ether). For $C_{24}H_{35}ClN_2O_6S_3$ (579·2) calculated: 49·77% C, 6·09% H, 6·12% Cl, 4·84% N, 16·61% S; found: 49·64% C, 6·57% H, 6·13% Cl, 4·85% N, 16·86% S.

10-(3-Methylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin (*IX*)

A mixture of 11·7 g 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], 16·0 g 2-methylpiperazine and 25 ml chloroform was refluxed for 7 h in a 100°C bath. After cooling, the chloroform was evaporated at reduced pressure and the residue divided between 80 ml benzene and 80 ml water. The benzene phase was washed with water and shaken with 80 ml 3M-HCl. The precipitated hydrochloride was filtered and suspended in the aqueous phase of the filtrate; treatment with NH_4OH liberated a base which was isolated by extraction with benzene; 11·9 g (84%) glassy substance. Neutralization with maleic acid in ethanol yields a maleate which, after recrystallization from ethanol–ether, melts at 163—167°C, after another recrystallization at 146—148°C. For $C_{24}H_{28}N_2O_4S_2$ (472·5) calculated: 61·01% C, 5·97% H, 5·93% N, 13·55% S; found: 61·12% C, 6·06% H, 5·80% N, 13·85% S.

8-Chloro-10-(*trans*-2,5-dimethylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepin (*XII*)

A mixture of 28·1 g 8,10-dichloro-10,11-dihydrodibenzo[*b*, *f*]thiepin[1], 45·0 g *trans*-2,5-dimethylpiperazine and 90 ml chloroform was processed like in the preceding case. A total of 16·7 g (46%)

oil was obtained. It was dissolved in 35 ml ethanol and the solution was neutralized by adding 5·4 g maleic acid in 10 ml ethanol. On standing, 14·0 g maleate crystallized; after two crystallizations from aqueous ethanol it melted at 205—207°C (7·3 g). Decomposition of the maleate with NH_4OH liberated a base, which was isolated by extraction with benzene. After its evaporation, the base crystallized from light petroleum; m.p. 128—130°C. ^{1}H-NMR spectrum: δ 7·90 (mcs, J = 2·0 Hz, 1 H, 9-H), 6·90—7·70 (m, 6 H, remaining aromatic protons), 3·00—4·20 (m, 3 H, $ArCH_2CHAr$), 2·00—3·10 (m, 6 H, 2 NCH_2 and 2 NCH of piperazine), 1·42 (s, 1 H, NH), 1·12 and 0·90 (2 d, J = 5·0 and 6·0 Hz, 6 H, 2 C—CH_3). For $C_{20}H_{23}ClN_2S$ (358·9) calculated: 66·92% C, 6·46% H, 9·88% Cl, 7·80% N, 8·93% S; found: 67·12% C, 6·53% H, 10·17% Cl, 7·62% N, 8·97% S.

Maleate prepared from the crystalline base melts at 218—219°C under decomposition (ethanol). For $C_{24}H_{27}ClN_2O_4S$ (475·0) calculated: 60·68% C, 5·73% H, 7·46% Cl, 5·90% N, 6·75% S; found: 61·05% C, 6·03% H, 7·00% Cl, 5·44% N, 6·49% S.

10-(*trans*-2,5-Dimethylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin (*XV*)

A mixture of 11·7 g 10-chloro-8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin[3], 20·6 g *trans*-2,5-dimethylpiperazine and 30 ml chloroform was processed like in the preceding cases. A total of 6·40 g (43%) oil was obtained which was dissolved in 15 ml ethanol and the solution was left to stand for 20 h; 0·16 g compound melting at 245—255°C precipitated; it was recrystallized from toluene, m.p. 270—274°C (prisms softening at 260°C). According to analysis it is *trans*-2,5-dimethyl-1,4-bis[8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin-10-yl]piperazine (*XVI*). For C_{36} . . $H_{38}N_2S_4$ (626·7) calculated: 68·99% C, 6·11% H, 4·47% N, 20·43% S; found: 69·57% C, 6·14% H, 4·27% N, 19·34% S. The filtrate after the preceding compound was neutralized under boiling by the addition of 1·8 g maleic acid. On standing overnight, 6·0 g crude maleate of base *XV* precipitated and was recrystallized from aqueous ethanol to melt at 212—214°C under decomposition. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·90—7·70 (m, 7 H, aromatic protons), 6·06 (s, 2 H, CH= =CH of maleic acid), 2·50—4·00 (m, $ArCH_2CHAr$, 2 NCH_2 and 2 NCH of piperazine), 2·39 (s, 3 H, SCH_3), c. 1·15 (m, 6 H, 2 C—CH_3). For $C_{25}H_{30}N_2O_4S_2$ (486·5) calculated: 61·71% C, 6·22% H, 5·76% N, 13·16% S; found 61·78% C, 6·30% H, 5·69% N, 12·92% S.

10-(4-Formyl-3-methylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin (*X*)

A solution of 2·7 g crude base *IX* in 20 ml ethyl formate was heated for 4 h in an autoclave at 130—140°C. After evaporation of the volatile components, a total of 2·7 g (93%) amorphous product was obtained, according to chromatography on a thin layer practically homogeneous. It was used for reduction in this form.

8-Chloro-10-(*trans*-4-formyl-2,5-dimethylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepin (*XIII*)

Like in the preceding case, reaction of 2·7 g crystalline base *XII* with 20 ml ethyl formate yielded 2·9 g (99%) glassy product which crystallized slowly from a mixture of benzene and light petroleum; m.p. 169—171°C. IR spectrum (Nujol): 775, 812, 860 (4 and 2 adjacent and solitary Ar—H), 1660 ($CONR_2$), 2720 cm^{-1} (N—CH_2). For $C_{21}H_{23}ClN_2OS$ (386·9) calculated: 65·18% C, 5·99 H, 9·17% Cl, 7·24% N, 8·29% S; found: 65·14% C, 6·10% H, 9·32% Cl, 6·73% N, 8·30% S.

10-(3,4-Dimethylpiperazino)-8-methylthio-10,11-dihydrodibenzo[*b*, *f*]thiepin (*XI*)

Crude amide *X* (4·6 g) was reduced with 2·1 g $LiAlH_4$ in a mixture of 50 ml ether and 20 ml tetrahydrofuran like in the preparation of *II*. A total of 3·78 g (86%) glassy base was obtained which was neutralized with maleic acid (1·1 g) in ethanol and thus converted to maleate, melting at 162–163°C (aqueous ethanol). For $C_{25}H_{30}N_2O_4S_2$ (486·6) calculated: 61·70% C, 6·21% H, 5·76% N, 13·18% S; found: 61·72% C, 6·22% H, 5·90% N, 13·18% S.

8-Chloro-10-(*trans*-2,4,5-trimethylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepin (*XIV*)

Like in the preceding case, 1·7 g amide *XIII* was reduced with 0·90 g $LiAlH_4$ in a mixture of 20 ml tetrahydrofuran and 10 ml ether. Analogously, 1·33 g (81%) glassy base was obtained which was treated with hydrogen chloride in a mixture of ethanol and ether to convert it to the hydrochloride. Crystallization from aqueous ethanol yielded a product melting at 208–210°C the analysis of which indicates that it is a mixture of mono-and dihydrochlorides. Decomposition with NH_4OH and isolation of the product by extraction with benzene yielded again an amorphous base, the identity of which was checked by the ^1H-NMR spectrum: δ 6·90–7·80 (m, 7 H, aromatic protons), 3·70–4·25 (m, 2 H, $ArCH_2$), 2·80–3·20 (m, 1 H, Ar—CH—N), 1·70–2·80 (m, 2 NCH_2, 2 NCH and NCH_3), 0·70–1·15 (m, 6 H, 2 C—CH_3).

5,5-Dimethyl-10-(4-methylpiperazino)-10,11-dihydro-5*H*-dibenzo[*b*, *f*]silepin (*XVII*)

A mixture of 6·0 g 5,5-dimethyl-10,11-dihydro-5*H*-dibenzo[*b*, *f*]silepin[33] (*XVIII*, b.p. 122 to 126°C/0·3 Torr), 4·5 g N-bromosuccinimide, 0·1 g benzoyl peroxide and 25 ml tetrachloromethane was stirred in a nitrogen atmosphere for 2 h at 50°C, illuminating with a 150 W bulb[31]. The succinimide precipitated after cooling was filtered, the filtrate combined with 20 ml 1-methylpiperazine and the mixture was refluxed for 4 h. After cooling, the mixture was divided between water and benzene, the benzene layer was washed with water, made alkaline with 10% solution of Na_2CO_3 and the base was isolated by extraction with benzene; 4·65 g (55%) oil. Neutralization with 1·6 g maleic acid in ethanol and addition of ether yielded a dimaleate crystallizing from a mixture of ethanol and ether: m.p. 96–98°C. For $C_{29}H_{36}N_2O_8Si$ (568·7) calculated: 61·25% C, 6·38% H, 4·93% N; found: 60·62% C, 6·47% H, 4·78% N. Decomposition of this salt by treatment with alkali yielded a base which was isolated by extraction with ether. ^1H-NMR spectrum: δ 6·90–7·80 (m, 8 H, aromatic protons), 3·35 (t, J = 6·0 Hz, 1 H, Ar—CH—N), 3·25 (d, J = 6·0 Hz, 2 H, $ArCH_2$), 1·85–2·65 (m, 8 H, 4 NCH_2 of piperazine), 2·11 (s, 3 H, NCH_3), 0·46 (s, 6 H CH_3—Si—CH_3).

Evaporation of the benzene phase after shaking with 1M-HCl yielded 2·8 g oil which was distilled to 1·3 g crude 5,5-dimethyl-5*H*-dibenzo[*b*, *f*]silepin (*XX*), b.p. 110–120°C/0·2 Torr. This boiling point agrees with that in ref.[33] (116·5–117·5°C/0·2 Torr) but the ^1H-NMR spectrum indicates the presence of contaminants; besides a multiplet of aromatic protons and a singlet of $Si(CH_3)_2$ (about 0·5 p.p.m.) there are low signals at 2·93, 3·00 and 3·11 p.p.m.

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REFERENCES

1. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
2. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
3. Pelz K., Jirkovský I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1895 (1968).
4. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
5. Jílek J. O., Šindelář K., Dlabač A., Kazdová E., Pomykáček J., Šedivý Z., Protiva M.: This Journal *38*, 1190 (1973).

6. Jílek J. O., Metyšová J., Protiva M.: This Journal *39*, 3153 (1974).
7. Jílek J. O., Metyšová J., Němec J., Šedivý Z., Pomykáček J., Protiva M.: This Journal *40*, 3386 (1975).
8. Jílek J. O., Červená I., Kopicová Z., Šindelář K., Svátek E., Metyšová J., Dlabač A., Pomykáček J., Protiva M.: This Journal *41*, 443 (1976).
9. Fouché J. C. L., Gaumont R., Gueremy C. G. A. (Rhone-Poulenc A. S.): Brit. 1 157 246; Neth. Appl. 68/4·846 (Fr. Appl. 14. IV. 1967); Chem. Abstr. *71*, 70·634 (1969).
10. Schindler W., Schmid E., Züst A. (J. R. Geigy A. - G.): Swiss 493 558 (Appl. 21. II. 1968); Fr. Demande 2,002.326; Ger. Offen. 1 908 545; Neth. Appl. 69/2 285; Chem. Abstr. *72*, 111·529 (1970).
11. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
12. Sen A. B., Shanker K.: J. Prakt. Chem. *302*, 10 (1965).
13. Edgell W. F., Parts L.: J. Amer. Chem. Soc. *77*, 4899 (1955).
14. Queisnerová M., Svátek E., Metyšová J.: Biochem. J. *114*, 339 (1969).
15. Franc Z., Horešovský O., Pelc B., Francová V.: Biochem. Pharmacol. *19*, 1443 (1970).
16. Jílek J. O., Metyšová J., Svátek E., Jančik F., Pomykáček J., Protiva M.: This Journal *38*, 599 (1973).
17. Kuntzman R., Phillips A., Tsai I., Klutch A., Burns J. J.: J. Pharmacol. Exp. Ther. *155*, 337 (1967).
18. Gilman N. W., Sternbach L. H.: J. Heterocycl. Chem. *8*, 297 (1971).
19. Kamm J. J., Szuna A., Kuntzman R.: J. Pharmacol. Exp. Ther. *182*, 507 (1972).
20. Kamm J. J., Szuna A.: J. Pharmacol. Exp. Ther. *184*, 729 (1973).
21. Mann F. G.: J. Chem. Soc. *1934*, 461.
22. Ward K. jr: J. Amer. Chem. Soc. *57*, 914 (1935).
23. Jones E. R. H., Wilson W.: J. Chem. Soc. *1949*, 547.
24. Bercz C. V., Ice R. D.: J. Pharm. Sci. *61*, 1316 (1972).
25. Robinson C. B., Herbrandson H. F.: J. Amer. Chem. Soc. *94*, 7883 (1972).
26. Beck K. M., Hamlin K. E., Weston A. W.: J. Amer. Chem. Soc. *74*, 605 (1952).
27. Pollard C. B., Lauter W. M., Duff J. G.: J. Org. Chem. *24*, 1175 (1959).
28. Seidlová V., Protiva M.: This Journal *32*, 1747 (1967).
29. Seidlová V., Pelz K., Adlerová E., Jirkovský I., Metyšová J., Protiva M.: This Journal *34*, 2258 (1969).
30. Šindelář K., Metyšová J., Protiva M.: This Journal *34*, 3801 (1969).
31. Corey J. Y., Dueber M., Bichlmeir B.: J. Organometal. Chem. *26*, 167 (1971); Chem. Abstr. *74*, 100·150 (1971).
32. Cartledge F. K., Mollere P. D.: J. Organometal. Chem. *26*, 175 (1971); Chem. Abstr. *74*, 100·154 (1971).
33. Barton T. J., Volz W. E., Johnson J. L.: J. Org. Chem. *36*, 3365 (1971).
34. Šindelář K., Metyšová J., Protiva M.: This Journal *38*, 2137 (1973).
35. Valenta V., Metyšová J., Šedivý Z., Protiva M.: This Journal *39*, 783 (1974).
36. Schneider J. (Wander A.-G.): Ger. Offen. 2 316 438 (Swiss Appl. 4. IV. 1972); Chem. Abstr. *80*, 14 969 (1974).

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